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| 09/480,544 | 01/10/2000 | JOHN H. KENTEN | 0039096-0030 | 4434 |

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| EXAMINER | |
|---|---|
| CHAKRABARTI, ARUN K | |
| ART UNIT | PAPER NUMBER |
| 1634 | 16 |

DATE MAILED: 12/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/480,544 | Applicant(s) Kenten et al. |
|---|---|---|
| | Examiner Arun Chakrabarti | Art Unit 1634 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Dec 12, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *32-43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *32-43* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

## DETAILED ACTION

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 32-43 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Malek et al. (U.S. Patent 5,130,238) (July 14, 1992) in view of Kenten et al (U.S. Patent 6,174,709 B1) (January 16, 2001).

Malek et al teaches a process for the detection of a specific nucleic acid sequence (Abstract and Figure 1A), comprising the steps of:

(a) the sample (claim 1, column 22, lines 57-58) comprising

(I) a first oligonucleotide primer (claim 1, column 22, line 59) ,

(ii) a second oligonucleotide primer comprising an antisense sequence of a promoter (claim 1, column 22, lines 60-61),

(iii) a DNA-directed RNA polymerase that recognizes the promoter (claim 1, column 22, lines 62-63),

(iv) an RNA-directed DNA polymerase (claim 1, column 22, lines 64),

(v) a DNA-directed DNA polymerase (claim 1, column 22, lines 65),

(vi) a ribonuclease that hydrolyzes RNA of an RNA-DNA hybrid without hydrolyzing single or double-stranded DNA (claim 1, column 22, lines 66-68),

(b) incubating the reaction mixture for a sufficient time to amplify the specific nucleic acid sequence to form an amplified nucleic acid sequence mixture comprising an amplified nucleic acid sequence (claim 1, column 23, lines 4-8);

Malek et al teaches a process wherein

(I) the first oligonucleotide primer hybridizes to the RNA first template (claim 1, column 23, lines 9-10),

(ii) the RNA-directed DNA polymerase uses the RNA first template to synthesize a DNA second template by extension of the first oligonucleotide primer and thereby forms an RNA-DNA hybrid intermediate (claim 1, column 23, lines 11-15),

(iii) the ribonuclease hydrolyses RNA which comprises the RNA-DNA hybrid intermediate (claim 1, column 23, lines 16-17),

(iv) the second oligonucleotide primer hybridizes to the DNA second template (claim 1, column 23, lines 18-19),

(v) the DNA-directed DNA polymerase uses the second oligonucleotide primer as template to synthesize the promoter by extension of the DNA second template (claim 1, column 23, lines 20-23),

(vi) the DNA-directed RNA polymerase recognizes the promoter and transcribes the second template, thereby providing copies of the RNA first template (claim 1, column 23, lines 24-27); and thereafter

c) maintaining the conditions for a time sufficient to achieve a desired amplification of the specific nucleic acid sequence (claim 1, column 23, lines 28-31).

Malek et al teaches a process wherein step (b) comprises adding to the reaction medium single-stranded DNA which comprises an antisense sequence of the promoter (Claim 10, lines 59-65).

Malek et al teaches a process wherein step (b) comprises adding to the reaction medium and RNA-DNA hybrid comprising the single-stranded DNA, such that the ribonuclease hydrolyzes RNA which comprises the RNA-DNA hybrid (Claim 5, column 24, lines 25-29).

Malek et al teaches a process wherein step (b) comprises adding to the reaction medium single-stranded DNA which comprises the DNA second template, such that

(I) the second oligonucleotide primer hybridizes to the single-stranded DNA (claim 6, column 24, lines 34-35),

(ii) the DNA-directed DNA polymerase uses the second oligonucleotide primer as template to synthesize the promoter by extension of the DNA second template (claim 6, column 24, lines 36-39), and

(iii) the DNA-directed RNA polymerase recognizes the promoter and transcribes the DNA second template, thereby providing copies of the RNA first template (claim 6, column 24, lines 40-43).

Malek et al teaches a process wherein step (b) comprises adding to the reaction medium a DNA comprising the promoter, such that the DNA-directed RNA polymerase transcribes the DNA, thereby synthesizing the single-stranded RNA (claim 8, column 24, lines 49-53).

Malek et al teaches a process wherein step (b) comprises adding to the reaction medium a DNA comprising the promoter, such that the DNA-directed RNA polymerase transcribes the DNA, thereby synthesizing the single-stranded RNA ( claim 9, column 24, lines 54-58).

Malek et al teaches a process wherein the RNA-directed DNA polymerase is a retrovirus reverse transcriptase (claim 30, column 26, lines 4-6).

Malek et al teaches a process wherein the DNA-directed DNA polymerase lacks exonuclease activity (claim 33, column 26, lines 13-15).

Malek et al teaches a process wherein all DNA polymerase in the reaction medium lack exonuclease and DNA endonuclease activity (claim 34, column 26, lines 16-18).

Malek et al teaches a process wherein the DNA-directed DNA polymerase is DNA polymerase alpha or DNA polymerase beta.

Malek et al does not teach the addition of;

(I) at least one probe sequence complementary to the RNA first template labeled with an electrochemiluminescent species comprising ruthenium-tris-bipyridine,

(ii) at least one second capture probe sequence complementary to the RNA first template labeled with a binding species selected from biotin,

(iii) a bead coated with a complementary binding species to the second probe sequence; and thereafter

(d) providing conditions of temperature and buffer to allow the hybridization of the probes to the first RNA template and the binding of the binding species on the second capture probe with the complementary binding species on the bead to form a bead bound complex; and then

(e) detecting the bead bound complex using the electrochemiluminescent species.

Kenten et al teaches the addition of;

(I) at least one probe sequence complementary to the RNA first template labeled with an electrochemiluminescent species comprising ruthenium-tris-bipyridine (Example I),

(ii) at least one second capture probe sequence complementary to the RNA first template labeled with a binding species selected from biotin (Examples IV-V)

(iii) a streptavidin-coated magnetic bead with a complementary binding species to the second probe sequence (Examples IV-V); and thereafter

(d) providing conditions of temperature and buffer to allow the hybridization of the probes to the first RNA template and the binding of the binding species on the second capture probe with

the complementary binding species on the bead to form a bead bound complex (Example V); and then

(e) detecting the bead bound complex using the electrochemiluminescent species.(Example V).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the detection of hybridization by bead bound complex with electrochemiluminescent species model of Kenten et al. in the enhanced nucleic acid amplification method of Malek et al. since Kenten et al. states , "The unexpected exponential amplification of the invention greatly simplifies the process of amplifying multiple nucleic acid sequences of interest present in a sample (Column 5, lines 1-4)". An ordinary practitioner would have been motivated to combine the detection of hybridization by bead bound complex with electrochemiluminescent species model of Kenten et al. in the enhanced nucleic acid amplification method of Malek et al in order to achieve the express advantages noted by Kenten et al. of a system which provides unexpected exponential amplification that greatly simplifies the process of amplifying multiple nucleic acid sequences of interest present in a sample.

***Response to Arguments***

3. Applicant's arguments with respect to all pending claims have been considered but are they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Kenten et al since Kenten et al. states , "The unexpected exponential amplification of the invention greatly simplifies the process of amplifying multiple nucleic acid sequences of interest present in a sample (Column 5, lines 1-4)".

Applicant then argues the 103 rejection is improper because it is obvious to try and lacks a reasonable expectation of success.

With regard to the " lacks a reasonable expectation of success." argument, The MPEP 2143.02 states "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could

not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Kenten reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different ECL labels were actually experimentally studied and found to be functional to monitor the amplification activity (Examples 1-7). This evidence of functionality trumps the attorney arguments, which argues that Kenten reference is an invitation to research, since Kenten steps beyond research and shows the functional product.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., (a) the invention does not require sample pretreatment and (b) the detection of **unlabeled** amplification products through the use of two probes, one having ECL label and the other having a capture moiety) are not recited in the rejected claim(s). Although the claims are interpreted in light of the

specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also argues that PCR and NASBA are two different methods because PCR results in DNA, whereas NASBA results in RNA. This argument is not persuasive in view of the fact that RNA polymerase can also produce RNA via PCR reaction.

In response to applicant's argument that Kenten has motivation to use his invention which is different from the claimed invention, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

***Conclusion***

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

**Arun Chakrabarti,**

**Patent Examiner,**

**December 20, 2002**

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600